DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 12-813/S-029, S-043

Allergan, Inc,
Attention: Elizabeth Bancroft
Director, Worldwide Regulatory Affairs
2525 DuPont Drive
P.O. Box 19534
Irvine, CA 92713-9534

AUG 3 I998

Dear Ms. Bancroft:

Please refer to your supplemental new drug application dated December 5, 1996, received December 9,1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BLEPHAMIDE (sulfacetamide sodium-prednisolone acetate ophthalmic suspension) Sterile. We also refer to our letters dated January 2 and June 29, 1997.

We acknowledge receipt of your submissions dated July 10, 1997, and May 26, 1998.

The supplemental application provides for revised labeling of the package insert.

This supplement (043) supersedes supplement 029 which provided draft labeling to comply with the January 10, 1984, ***Federal Register Notice.***

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling submitted on May 26, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

This approval affects only the changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

If you have any questions, please contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

WAC 8/3/98

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

0260

ALLERGAN

APPROVED

AUG 1998

BLEPHAMIDE

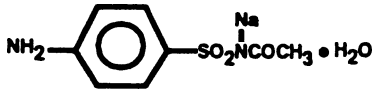
(sulfacetamide sodium-prednisolone acetate ophthalmic suspension)

sterile

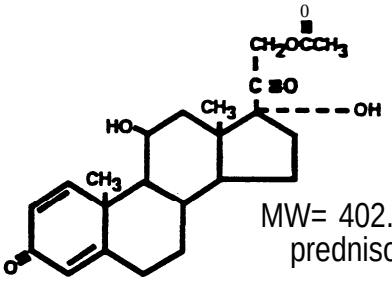
DESCRIPTION

BLEPHAMIDE ophthalmic suspension is a topical anti-inflammatory/anti-infective combination product for ophthalmic use.

Structural Formulas:



MW= 254.24 $C_8H_9NaO_3S$ •
sulfacetamide sodium



MW= 402.49 $C_{23}H_{30}O_6$
prednisolone acetate

Chemical Names:

Sulfacetamide sodium: N-sulfanilylacetamide monosodium salt monohydrate.

Prednisolone acetate: 11 B, 17, 21-trihydroxypregna-1, 4-diene-3, 20-dione 21-acetate

Contains:

Actives: sulfacetamide sodium 10% prednisolone acetate (microfine suspension) 0.2%.
Preservative: benzalkonium chloride (0.004%). Inactives: polyvinyl alcohol 1.4%; polysorbate 80; edetate disodium; sodium phosphate, dibasic; potassium phosphate, monobasic; sodium thiosulfate; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water.

CLINICAL PHARMACOLOGY

Corticosteroids suppress the inflammatory response to a variety of agents and they probably delay or slow healing. Since corticosteroids may inhibit the body's defense mechanism against infection, a concomitant antibacterial drug may be used when this inhibition is considered to be clinically significant in a particular case.

When a decision to administer both a corticosteroid and an antibacterial is made, the administration of such drugs in combination has the advantage of greater patient compliance and convenience, with the added assurance that the appropriate dosage of both drugs is administered. When both types of drugs are in the same formulation, compatibility of ingredients is assured and the correct volume of drug is delivered and retained. The relative potency of corticosteroids depends on the molecular structure, concentration and release from the vehicle.

Microbiology: Sulfacetamide sodium exerts a bacteriostatic effect against susceptible bacteria by restricting the synthesis of folic acid required for growth through competition with p-aminobenzoic acid.

Some strains of these bacteria may be resistant to sulfacetamide or resistant strains may emerge *in vivo*

The anti-infective component in these products is included to provide action against specific organisms susceptible to it. Sulfacetamide sodium is active *in vitro* against susceptible strains of the following microorganisms: *Escherichia coli Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus (viridans* group), *Haemophilus influenzae, Klebsiella* species and *Enterobacterspecies.* This product does not provide adequate coverage against: *Neisseria* species, *Pseudomonas* species, and *Serratia marcescens (see* INDICATIONS AND USAGE).

INDICATIONS AND USAGE

A steroid/anti-infective combination is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular corticosteroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of corticosteroid use in certain infective conjunctivitides is accepted to obtain diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular antibacterial drug in this product is active against the following common bacterial eye pathogens: *Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus (viridans group), Haemophilus influenzae, Klebsiella species,* and *Enterobacter* species. This product does not provide adequate coverage against: *Neisseria* species, *Pseudomonas* species, *Serratia marcescens.*

A significant percentage of staphylococcal isolates are completely resistant to sulfa drugs.

CONTRAINDICATIONS

BLEPHAMIDEophthalmic suspension is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

This product is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation, to other sulfonamides and to other corticosteroids. See WARNINGS. (Hypersensitivity to the antimicrobial component occurs at a higher rate than for other components.)

WARNINGS

NOT FOR INJECTION INTO THE EYE.

Prolonged use of corticosteroids may result in ocular hypertension/glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation.

Acute anterior uveitis may occur in susceptible individuals, primarily Blacks.

Prolonged use of BLEPHAMIDE ophthalmic suspension may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical corticosteroids. In acute purulent conditions of the eye, corticosteroids may mask infection or enhance existing infection.

If the product is used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Corticosteroids should be used with caution in the presence of glaucoma. Intraocular pressure should be checked frequently.

A significant percentage of staphylococcal isolates are completely resistant to sulfonamides.

The use of steroids after cataract surgery may delay healing and increase the incidence of filtering blebs.

The use of ocular corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of corticosteroidmedication in the treatment of herpes simplex requires great caution.

Topical steroids are not effective in mustard gas keratitis and Sjogren's keratoconjunctivitis.

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fuiminant hepatic necrosis, agranulocytosis, aplastic anemia and other Wood dyscrasias. Sensitization may recur when a sulfonamide is readministered, irrespective of the route of administration.

If signs of hypersensitivity or other serious reactions occur, discontinue use of this preparation. Cross-sensitivity among corticosteroids has been demonstrated (see ADVERSE REACTIONS).

PRECAUTIONS

General: The initial prescription and renewal of the medication order beyond 20 milliliters of the suspension should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate fluorescein staining. If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

The possibility of fungal infections of the cornea should be considered after prolonged corticosteroid dosing. Use with caution in patients with severe dry eye. Fungal cultures should be taken when appropriate.

The p-aminobenzoic acid present in purulent exudates competes with sulfonamides and can reduce their effectiveness.

Information for Patients: If inflammation or pain persists longer than 48 hours or becomes aggravated, the patient should be advised to discontinue use of the medication and consult a physician (see WARNINGS).

Contact lenses should not be worn during the use of this product.

This product is sterile when packaged. To prevent contamination, care should be taken to avoid touching the applicator tip to eyelids or to any other surface. The use of this bottle by more than one person may spread infection. Keep bottle tightly closed when not in use. Protect from light. Sulfonamide solutions darken on prolonged standing and exposure to heat and light. Do not use if solution has darkened. Yellowing does not affect activity. Keep out of the reach of children.

Laboratory Tests: Eyelid cultures and tests to determine the susceptibility of organisms to sulfacetamide may be indicated if signs and symptoms persist or recur in spite of the recommended course of treatment with BLEPHAMIDE ophthalmic suspension.

Drug Interactions: BLEPHAMIDE ophthalmic suspension is incompatible with silver preparations. Local anesthetics related to p-aminobenzoic acid may antagonize the action of the sulfonamides.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Prednisolone has been reported to be noncarcinogenic. Long-term animal studies for carcinogenic potential have not been performed with sulfacetamide.

One author detected chromosomal nondisjunction in the yeast *Saccharomyces cerevisiae* following application of sulfacetamide sodium. The significance of this finding to topical ophthalmic use of sulfacetamide sodium in the human is unknown.

Mutagenic studies with prednisolone have been negative. Studies on reproduction and fertility have not been performed with sulfacetamide. A long-term chronic toxicity study in dogs showed that high oral doses of prednisolone prevented estrus. A decrease in fertility was seen in male and female rats that were mated following oral dosing with another glucocorticosteroid.

Pregnancy:Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with sulfacetamide sodium. Prednisolone has been shown to be teratogenic in rabbits, hamsters, and mice. In mice, prednisolone has been shown to be teratogenic when given in doses 1 to 10 times the human ocular dose. Dexamethasone, hydrocortisone and prednisolone were ocularly applied to both eyes of pregnant mice five times per day on days 10 through 13 of gestation. A significant increase in the incidence of cleft palate was observed in the fetuses of the treated mice. There are no adequate well-controlled studies in pregnant women dosed with corticosteroids.

Kemicterus may be precipitated in infants by sulfonamides being given systemically during the third trimester of pregnancy. It is not known whether sutfacetamide sodium can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

BLEPHAMIDE ophthalmic suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Systemically administered sulfonamides are capable of producing kemicterus in infants of lactating women. Because of the potential

for serious adverse reactions in nursing infants from sulfacetamide sodium and prednisolone acetate ophthalmic suspensions, a decision should be made whether to discontinue nursing or to discontinue the medications.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of six have not been established.

ADVERSE REACTIONS

Adverse reactions have occurred with corticosteroid/antibacterial combination drugs which can be attributed to the corticosteroid component, the antibacterial component, or the combination. Exact incidence figures are not available since no denominator of treated patients is available.

Reactions occurring most often from the presence of the antibacterial ingredient are allergic sensitizations. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias (See WARNINGS).

Sulfacetamide sodium may cause local irritation.

The reactions due to the corticosteroid component in decreasing order of frequency are: elevation of intraocular pressure of with possible development of glaucoma and infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing.

Although systemic effects are extremely uncommon, there have been rare ocurrences of systemic hypercorticoidism after use of topical corticosteroids.

Corticosteroid-containing preparations can also cause acute anterior uveitis or perforation of the globe. Mydriasis, loss of accommodation and ptosis have occasionally been reported following local use of coticosteroids.

Secondary infection: The development of secondary infection has occurred after use of combinations containing corticosteroids and antibacteriais. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of corticosteroid. The possibility of fungal invasion must be considered in any persistent corneal ulceration where corticosteroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

DOSAGE AND ADMINISTRATION

SHAKE WELL BEFORE USING. Two drops should be instilled into the conjunctival sac every four hours during the day and at bedtime.

Not more than 20 milliliters should be prescribed initially, and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS above.

BLEPHAMIDE dosage may be reduced, but care should be taken not to discontinue therapy prematurely. In chronic ccriditions, withdrawal of treatment should be carried out by gradually decreasing the frequency of application.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated (see PRECAUTIONS).

HOW SUPPLIED

BLEPHAMIDE ophthalmic suspension is supplied in plastic dropper bottles in the following sizes:

5 mL - NDC 11980-022-05

10 mL - NDC 11980-022-10

Note: Protect from freezing. Shake well before using.

Storage: Store BLEPHAMIDE at 8-24C (46-75F) in an upright position.

PROTECT FROM LIGHT

Sulfonamide solutions darken on prolonged standing and exposure to heat and light. Do not use if solution has darkened. Yellowing does not affect activity.

KEEP OUT OF REACH OF CHILDREN

Rx only.

Revised February 1998

ALLERGAN AMERICA, Hormigueros, Puerto Rico 00660